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## REVIEW

# Midregional proadrenomedullin for prognosis in community-acquired pneumonia: A systematic review



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## KEYWORDS

Pneumonia;  
Meta-analysis;  
Prognosis;  
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## Summary

**Introduction:** The initial prognostic assessment of patients with community-acquired pneumonia (CAP) has important clinical implications. We hypothesized that midregional proadrenomedullin (MR-proADM) is a valuable test for the prediction of outcomes in patients with CAP. **Methods:** We performed a systemic review of the literature and a meta-analysis to evaluate the prognostic value of MR-proADM for short and long-term mortality in patients with CAP.

**Results:** Twelve studies were included in the systematic review. Elevated MR-proADM was associated with an increase in short-term mortality (OR = 6.8; 95% CI: 4.65–10.13; *P* value < 0.001) and complications (OR = 5.0; 95% CI: 3.86–6.49; *P* value < 0.001). The pooled analysis of 4 studies showed an improvement in the discriminant ability by 8% (95% CI: 2%–14%) when MR-proADM was added to CURB-65/CRB-65. Studies that reported long-term prognosis indicated an increased risk of death in patients with elevated MR-proADM.

**Conclusion:** Elevated level of MR-proADM is significantly associated with both short-term mortality and complications in patients with CAP. Studies also indicate that MR-proADM has prognostic value for prediction of long-term mortality in these patients. The addition of MR-proADM improves the discriminant ability of CURB-65/CRB-65.

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## Introduction

One of the most challenging tasks clinicians face when assessing patients with community-acquired pneumonia (CAP) is to risk stratify them. The initial risk stratification has important clinical implications. It is largely based on the stratification that clinicians decide on the setting to manage patients with CAP. To that end, clinicians have relied mainly on clinical judgment and clinical prediction rules.

In recent years, biomarkers have emerged that can help with the prediction of outcomes in patients with CAP. One that has been in the spotlight is midregional proadrenomedullin (MR-proADM), a peptide that was initially identified in plasma of patients with septic shock at high concentrations. MR-proADM is derived from the same precursor as adrenomedullin, which is a 52-amino acid peptide with important hemodynamic effects [1].

Although adrenomedullin cannot be reliably measured in the plasma due to its short half-life and physical properties, an immunoluminometric assay has been developed for the more stable MR-proADM [2]. The measurement of MR-proADM can thus serve as a proxy for the production of the more physiologically active adrenomedullin. Since the development of the assay, a number of studies have reported on the predictive value of MR-proADM in patients with CAP [3–7]. We thought that an objective and critical

appraisal of these studies is timely. We hypothesized that MR-proADM is a valuable test for the prediction of outcomes in patients with CAP. The primary aim of our study is to evaluate the literature on the prognostic value of MR-proADM for short and long-term mortality in patients with CAP. Secondary aims are to assess whether MR-proADM can predict short-term complications in patients with CAP and whether MR-proADM can improve the discriminant ability of a risk score. We carried out a systematic review and meta-analysis of the studies assessing MR-proADM in these patients.

## Methods

### Eligibility criteria

Studies that reported the prognostic value of MR-proADM for short and long-term mortality or complications in patients with CAP were eligible for inclusion in this systematic review.

### Exclusion criteria

Studies were excluded if the patient population was not composed solely of patients with CAP. We also excluded studies with duplicate patient cohorts. However, when two

studies using the same patient cohort reported on different outcomes (e.g. different time ascertainment), they were included in the systematic review but their data were not pooled in the same meta-analysis.

### Predictive variables

The main predictive variable was MR-proADM level. A commercially available test has been developed for the measurement of MR-proADM in the plasma (B.R.A.H.M.S MR-proADM KRYPTOR). This test is performed via sandwich immunoluminometric assay. Antibodies are employed against the 45-92 MR-proADM. The initial report of the test established that the lower detection limit was 0.08 nmol/L [2]. We also analyzed the discriminant ability of the confusion, urea, respiratory and blood pressure (CURB) score. The CURB score is based on severity criteria for pneumonia developed by the British Thoracic Society: confusion, urea  $\geq 7$  mmol/l, respiratory rate  $\geq 30$ /min, and blood pressure  $\leq 60$  mmHg. An early study showed that the presence of 2 of these criteria upon hospital admission is highly sensitive for the prediction of death in patients with CAP [8]. There are interactions of the CURB score such as the CURB-65, which also relies on age  $\geq 65$  years as a criterion and adds low systolic blood pressure ( $<90$  mmHg) to the blood pressure criterion, and CRB-65, which does not take urea into account [9,10].

### Outcomes

The primary outcome was short-term mortality. Studies that reported mortality on  $<3$  month follow-up or in-hospital mortality were included in this category. If a study reported the primary outcome in multiple time points, we chose the one that most closely approximated to 30 days. Another primary outcome was long-term mortality. Studies that reported mortality on follow-up of  $\geq 3$  months were included in this category. The secondary outcome was a composite of short-term complications. The latter included death plus one or a combination of following outcomes as reported in the primary studies: need for ICU admission, need for mechanical ventilation, respiratory failure, and other disease-specific complications.

### Search

Two investigators (KEL and EAA) independently performed a search in Pubmed and Embase through Feb/2013. For Pubmed, the search strategy included the following: ("Respiratory Tract Infections"[Mesh] OR "pneumonia"[All Fields]) AND ("Pro-adrenomedullin"[All Fields] OR "adrenomedullin"[All Fields] OR "Proadrenomedullin"[All Fields]). The Embase search strategy included the following: (pneumonia.mp OR respiratory.mp) AND (adrenomedullin.mp OR proadrenomedullin.mp OR proadrenomedullin.mp).

### Risk of bias

We used the following items to assess risk of bias: demographic characteristics, selection criteria, definition of

CAP, index test obtained early in the course of disease, description of execution of index test, establishment of test cutoff before analysis, pre-specified objectives, long-term follow up, and absence of commercial funding. These were derived from a number of documents [11–13].

### Data extraction

Two investigators (KEL and EAA) independently extracted data from the studies, and conflicts were resolved by a third investigator (RC). We used a structured form to extract data from the studies. Data extracted included study setting and design, patient characteristics, study objective, quality items, and numerical data. We extracted the 4 cell values of a diagnostic  $2 \times 2$  table for MR-proADM prediction of outcomes.

We also abstracted the reported MR-proADM area under the receiver operating characteristic curve (AUC) with corresponding 95% CI for the prediction of short-term mortality. In order to allow comparison of the discriminant ability with MR-proADM, we abstracted the AUC with 95% CI of the CURB-65 or CRB-65 as reported by the primary studies. For the purpose of this review, we use both the CURB-65 and the CRB-65 interchangeably. For the sake of simplicity, we designate them risk score.

For long-term prognosis, we abstracted the reported estimate (measure of association) providing information on the predictive value of MR-proADM for mortality. We preferentially abstracted the estimates that were adjusted for severity of disease or clinical prediction rules.

### Statistical analysis

We present the sensitivity and specificity of MR-proADM for in-hospital mortality. If a study reported data based on more than one threshold, we used data based on the threshold that was established *a priori*. We summarize these estimates in forest plots. We also provide pooled odds ratios of MR-proADM for both short-term mortality and complications.

In order to evaluate if MR-proADM provides additional discriminant ability when combined with CURB-65 or CRB-65, we calculated the ratio of risk score plus MR-proADM over risk score. We obtained the standard error (SE) of the ratio by calculating the SE of the log-AUC of risk score and the SE of log-AUC of MR-proADM plus risk score. The SE of the ratio was then obtained with a previously described method [14]. The SE of the AUC reported in the primary studies was derived from the 95% CI. When we were unable to obtain the 95% CI from the primary studies or after contact attempt with their authors, we calculated it by estimating the AUC SE with the method proposed by Hanley and McNeil [15]. We present pooled AUC ratio; a value above one indicates that the combined risk score plus MR-proADM provides better discriminant ability than the risk score alone.

We performed meta-analysis using a random-effects model [16]. This approach assumes that the effect estimates vary among the studies. We evaluated heterogeneity with a chi-squared test and the  $I^2$ . We considered heterogeneity to be present with a  $P$  value  $<0.1$ , or when the  $I^2$

was more than 30%. For the remainder of the analyses, we considered a  $P$  value  $<0.05$  statistically significant. We used Stata 10 (StataCorp LP; College Station, TX) and Review Manager 5.2 software [17] for statistical analysis.

For long-term mortality, we decided that meta-analysis would not be appropriate given the heterogeneity in how the data were reported. However, we abstracted the data as stated above, and we appraise the evidence in the discussion section.

## Results

Our search identified 213 citations. After removing duplicates, we were left with 182 articles. Based on screening of titles and abstracts, we exclude 160 citations. These were excluded mostly because they were review articles or letters to the editors or articles that clearly did not pertain to the topic of this review. We fully reviewed 22 articles. Of these, we excluded 10 articles. The reasons for exclusion included different outcome [18], patient population not exclusively composed of patients with CAP [19–23], and duplicate cohorts [24–26]. An additional article was present only in abstract form, which did not provide enough data for extraction for our review [27]. We included 12 articles in this review (see Fig. 1) [4–7,28–34]. Table 1 shows the characteristics of the studies.

### Primary outcomes

For short-term mortality, we pooled data from 9 studies, which included a total population of 4201 patients (see Fig. 2) [3–5,7,28,31–34]. There was significant increase in short-term mortality with elevated MR-proADM (OR = 6.8;

95% CI: 4.65–10.13;  $P$  value  $< 0.001$ ). There was no significant heterogeneity ( $P$  value = 0.187). The  $I^2$  value was 29%. However, the estimates of sensitivity and specificity ranged substantially. Even within studies that used similar thresholds of around 1.5–1.85, the sensitivity varied from 0.46 to 0.85. The specificity also varied within this set of studies, ranging from 0.64 to 0.86 (see Fig. 3).

Five studies reported on long-term-mortality [4,6,7,28,33]. They showed increased risk of mortality in patients with elevated MR-proADM although in the study by Huang et al. this effect was limited to patients with Pneumonia Severity Index (PSI) classes IV/V [28]. We summarize these studies in Table 2.

### Pooled AUC ratio for the prediction of short-term mortality

On its own, MR-proADM showed moderate to good discriminant ability, ranging from 0.72 to 0.89 across 9 studies [3–5,7,28,31–34]. Four studies reported the AUC for MR-proADM, risk score, and risk score plus MR-proADM [3,4,7,33]. The discriminant ability of MR-proADM on its own, and together with the risk score in these 4 studies, is shown in Table 3. The pooled ratio of risk score plus MR-proADM over risk score was 1.08 (95% CI: 1.02–1.14;  $P$  value = 0.006; homogeneity test  $P$  value = 0.8;  $I^2$  value = 0%). Fig. 4 shows forest plot of the meta-analysis.

### Short-term complications

For the composite outcome of short-term complications, we pooled data from 5 studies (see Fig. 5) [3,4,29,30,34]. There was significant increase in short-term complication

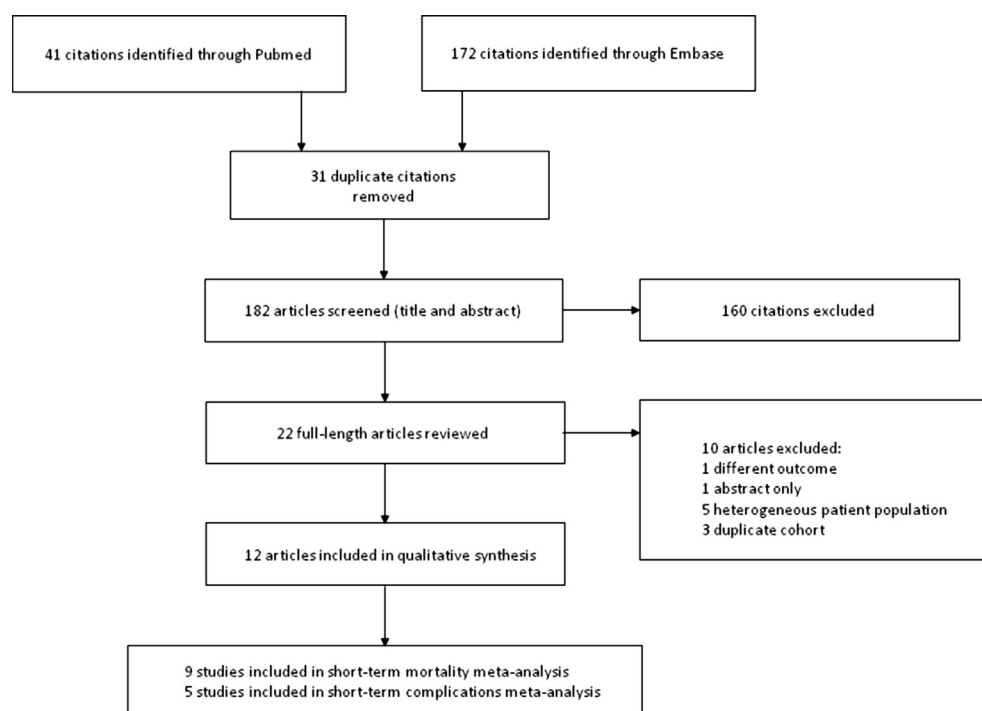


Figure 1 Flow chart of the search process for studies.

**Table 1** Characteristics of the studies included in this review.

Author, year	Study setting	Study design	Patient population	Patients, n	Age, yr	Male, %	Aim	Mortality, %
Christ-Crain, 2006 [5]	Switzerland, 2003–2005	Prospective cohort	Adults with CAP in the ED	302	69.6 (Mean)	61.9	Assessment of prognostic factors and biomarkers in CAP	12.6 (follow-up; mean 6.9 weeks)
Huang, 2009 [28]	US, 2001–2003	Prospective cohort	Adults with CAP in the ED	1653	65 (Mean)	52	Determine the pattern and prognostic role of MR-proADM in CAP	6.4 (30 days) 7.2 (48 days) 9.8 (90 days)
Kruger, 2010 [7]	Germany	Prospective cohort	Adults with CAP	728	59 (Mean)	59	Validate the predictive value of biomarkers in CAP	2.5 (28 days) 5 (180 days)
Guertler, 2011 [6]*	Switzerland, 2006–2008	Prospective cohort	Adults with CAP	877	73** (Median)	58.4**	Evaluate the prognostic value of PSI and biomarkers in CAP	17.3 (18 months)
Albrich, 2011 [3]*	Switzerland, 2006–2008	Prospective cohort	Adults with CAP	925	73** (Median)	57.5**	Evaluate the prognostic value of biomarkers in lower respiratory tract infection	5.4 (30 days)
Bereciartua Urbieto, 2011 [29]	Spain, 2008–2009	Prospective cohort	Adults with CAP admitted through the ED	250	71.1 (Mean)	68.4	Evaluate if biomarkers can predict bad outcomes in patients with CAP	8 (in-hospital)
Bello, 2012 [4]	Spain	Prospective cohort	Adults with CAP admitted through the ED	228	73 (Median)	61	Predictive value of biomarkers in adults with CAP	5.8 (30 days) 9.1 (90 days) 11.9 (180 days)
Kolditz, 2012 [30]	Germany	Prospective cohort	Hospitalized adults with CAP	51	72 (Median)	49	Evaluate the prognosis of biomarkers for ICU admission or mortality	12 (1 year) 12 (7 days)
Suberviola, 2012 [31]	Spain, 2009	Prospective cohort	Patients aged 17 yo or above admitted to ICU with CAP and severe sepsis or septic shock	49	59.4 (Mean)	67.3	Predictive value of proADM for mortality in patients with CAP. Compare the prognostic value of biomarkers and scores.	35 (in-hospital)
Courtais, 2013 [32]	France, 2009–2010	Prospective cohort	Adults with CAP presenting to ED	109	70.5 (Median)	63	Prognostic value of MR-proADM in patients with	8.3 (30-days)

(continued on next page)

Table 1 (continued)

Author, year	Study setting	Study design	Patient population	Patients, n	Age, yr	Male, %	Aim	Mortality, %
Julian-Jimenez, 2013 [33]	Spain, 2011–2012	Prospective cohort	Patients over 14 yo with CAP who presented to an urgent care facility	127***	65.8 (Mean)	58.3	CAP presenting to the ED Predictive value of biomarkers for short and mid-term mortality in patients with CAP	8.3 (in-hospital) 10.3 (30-days) 22.6 (180 days)
Lacoma, 2013 [34]	Spain	Prospective cohort	Patients presenting to ED with pneumonia for which blood culture was obtained	85	n.a.	69.4	Correlate biomarkers with mortality risk scores.	(30 days)

CAP, community-acquired pneumonia; ED, emergency department; MR-proADM, midregional proadrenomedullin.

\*Same patient cohort; \*\*demographic data included patients with lower respiratory tract infection; \*126 analyzed.

with elevated MR-proADM (OR = 5.0; 95% CI: 3.86–6.49;  $P$  value < 0.001). There was no significant heterogeneity ( $P$  value = 0.624). The  $I^2$  value was 0%. The sensitivity ranged from 0.62 to 0.80, while the specificity ranged from 0.53 to 0.86 (see Fig. 6).

### Risk of bias

Nine quality items were assessed; more than half of the studies did not complete 3 of these items. Table 4 and Fig. 7 summarize the findings of risk of bias assessment.

### Sensitivity analysis

We performed sensitivity analysis for short-term mortality according to 2 items in which most studies showed a high risk of bias. The pooled OR was 7.75 (95% CI: 4.72–12.70;  $P$  value < 0.001) in studies that did not establish a test cut-off *a priori* [3–5,7,31–34], and 5.27 (95% CI: 3.50–7.92;  $P$  value < 0.001) in the study that established it *a priori* [28]. The pooled OR was 7.05 (95% CI 4.13–12.03;  $P$  value < 0.001) in studies that had commercial funding [4,5,7,28,32,34], and 7.25 (95% CI 3.20–16.42;  $P$

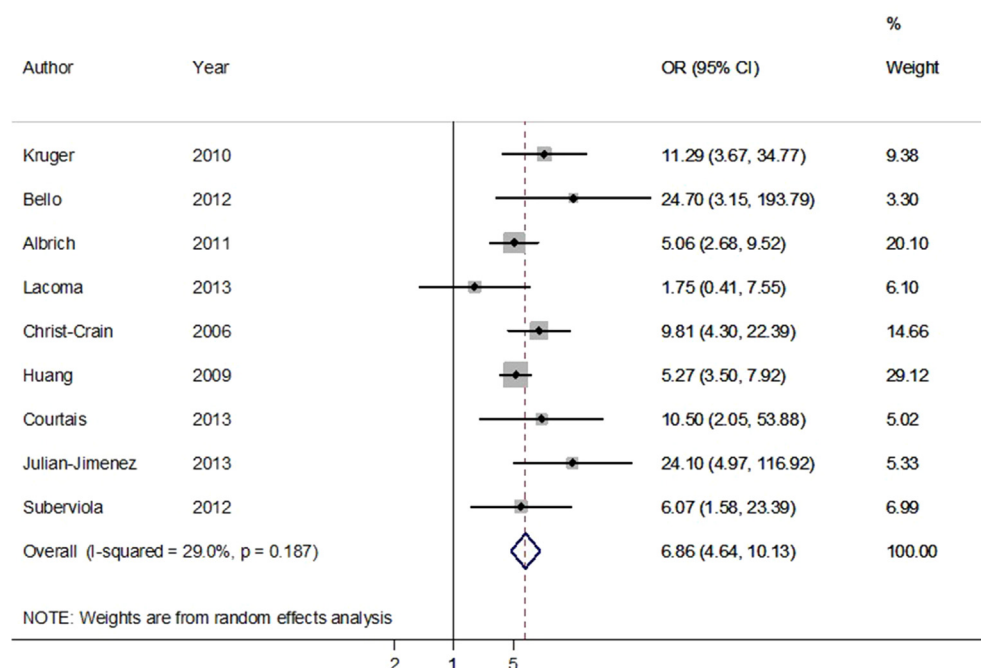
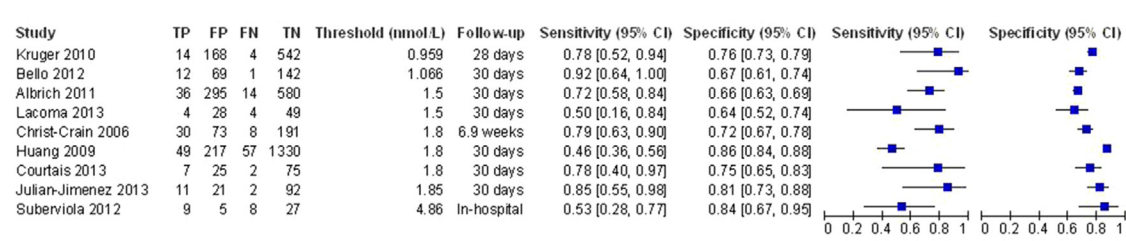


Figure 2 Forest plot displaying meta-analysis of the odds ratio of short-term mortality in patients with increased level of midregional proadrenomedullin.





**Figure 3** Forest plots displaying sensitivity and specificity of midregional proadrenomedullin for the prediction of short-term mortality in patients with community-acquired pneumonia.

value < 0.001) in studies that were free of commercial funding [3,31,34].

## Discussion

The main finding of our study is that an increased level of MR-proADM was associated with an increase in the odds of both short-term death and the composite outcome of complications in patients with CAP. The direction of the measure was consistent across all studies. The relatively

narrow confidence intervals indicate high precision of the pooled results. However, the individual studies showed variation in the accuracy of the test for short-term mortality. The sensitivity of the test, for instance, ranged from 0.46 to 0.92. Two studies with low sensitivity had a low sample size [31,34], and one of them used a very high test cut-off [31]. On the other hand, the study by Huang et al. also showed a low sensitivity in spite of a large sample size and establishment of the test cut-off *a priori* [28]. The specificity of the test was more consistent across the studies.

**Table 2** Long-term midregional proadrenomedullin prediction of mortality in patients with community-acquired pneumonia.

Author, year	Cutoff (nmol/L)	Estimate	Adjustment	Outcome
Huang, 2009 [28]	1.45	Subjects in the highest MR-proADM quartile had higher mortality than those in the quartile 1 –3 (33% vs 14%; <i>P</i> value < 0.001)	Not available	90-day mortality
Kruger, 2010 [7]	Not available	Significant increase in the hazard of death for every one unit increase in MR-proADM(log10) (HR = 1.9; 95% CI: 1.3 –2.8; <i>P</i> value = 0.0012)	CURB-65, comorbidity	180-day mortality
Guertler, 2011 [6]	1.97	Significant increase in the hazard of death for patients with MR-proADM > 1.97 compared with those with MR-proADM < 0.83 (HR = 3.3; 95% CI 1.7 –6.2; <i>P</i> value < 0.001)	gender, chills, age, comorbidities, and crp	18-month mortality
Bello, 2012 [4]	Not available	CURB-65 + MR-proADM AUC: 0.870 (95% CI: 0.806–0.920); <i>P</i> value < 0.001	CURB-65	1-year mortality
Julian-Jimenez, 2013 [33]	Not available	CURB-65 + MR-proADM AUC: 0.928 (95% CI: 0.855–1.0); <i>P</i> value < 0.001 PSI + MR-proADM AUC: 0.942 (95% CI: 0.899 –0.986); <i>P</i> value < 0.001	CURB-65	180-day mortality

MR-proADM, midregional proadrenomedullin; HR, hazard ratio; CURB-65, confusion, urea, respiratory, blood pressure score, and age; PSI, Pneumonia Severity Index.

**Table 3** Midregional proadrenomedullin (MR-proADM) and risk score area under the receiver operating characteristic curve with corresponding 95% CI for the prediction of short-term mortality.

	Kruger, 2010 <sup>a</sup> [7]	Albrich, 2011 <sup>b</sup> [3]	Bello, 2012 <sup>b</sup> [4]	Julian-Jimenez, 2013 <sup>b</sup> [33]
Relative increase in AUC with combined MR-proADM + risk score as compared to risk score alone, estimate (95% CI)	16% (−7%–46%)	11% (−1%–24%)	6% (−2%–14%)	7% (−5%–20%)
MR-proADM + risk score, estimate (95% CI)	0.85 (0.74–0.96)	0.8 (0.73–0.86)	0.90 (0.853–0.936)	0.934 (0.855–1.0)
Risk score alone, estimate (95% CI)	0.73 (0.6–0.86)	0.72 (0.66–0.77)	0.851 (0.798–0.895)	0.874 (0.804–0.964)
MR-proADM, estimate (95% CI)	0.85 (0.74–0.96)	0.76 (0.68–0.83)	0.859 (0.807–0.902)	0.892 (0.811–0.974)

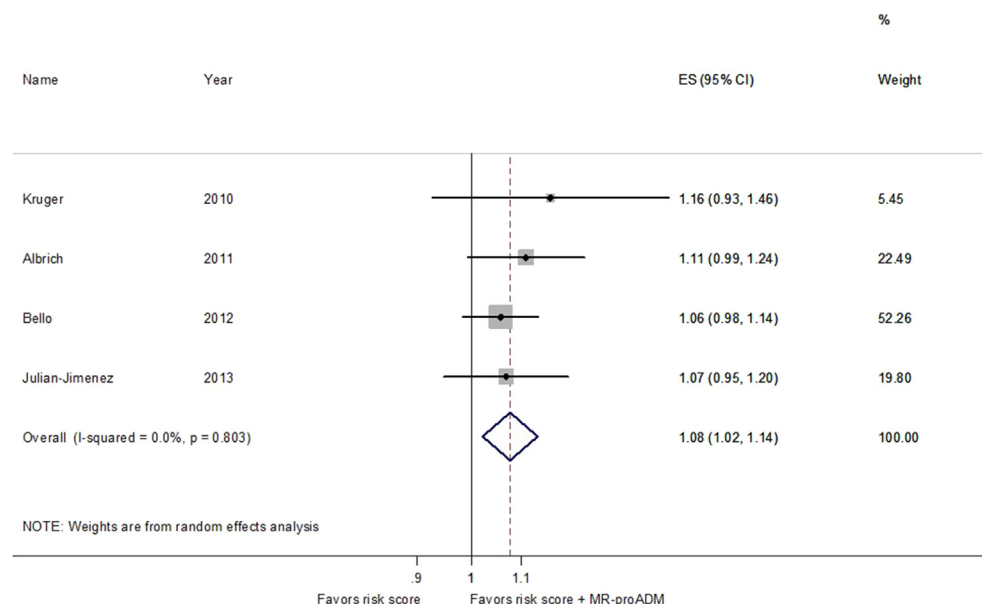
<sup>a</sup> CRB-65, confusion, respiratory, blood pressure, and age score.

<sup>b</sup> CURB-65, confusion, urea, respiratory, blood pressure, and age score.

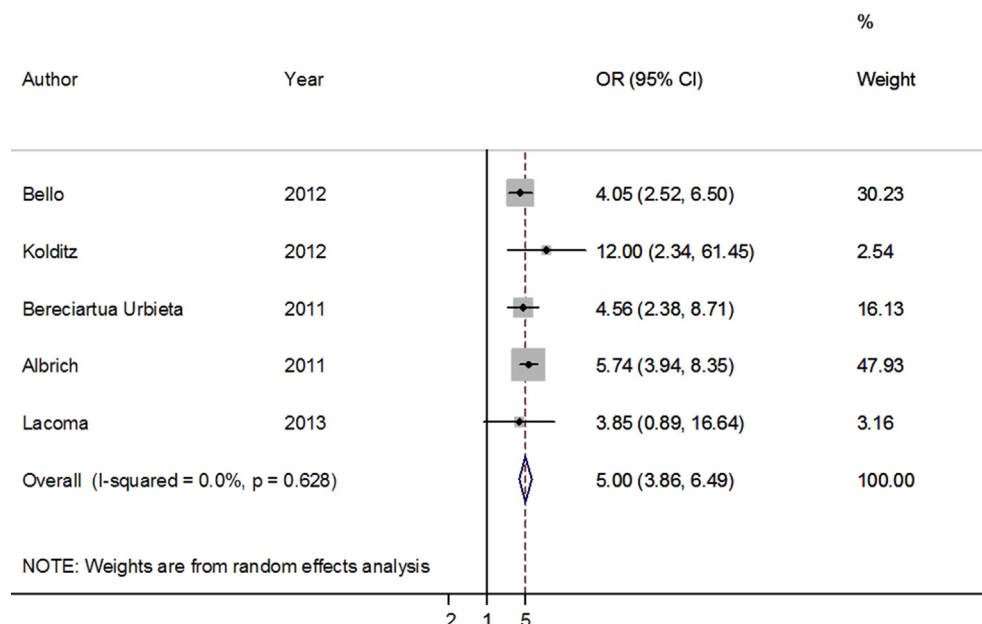
A clinically relevant question is whether MR-proADM adds discriminant ability to an established risk score. A prior meta-analysis by Loke et al. showed a CURB-65 diagnostic OR for death of 6.40 [35], an estimate that is similar to one we found for MR-proADM. This finding supports the notion that they are both similarly accurate for the prediction of death and could perhaps be used interchangeably. However, our analysis also suggests that a better approach may be the combined use of MR-proADM to CURB-65/CRB-65 since their association led to improved discriminant ability over that of the risk score alone.

Although the data for long-term prognosis is more scant, the available evidence also seems to indicate an increased risk of mortality in patients with CAP presenting with high level of MR-proADM. In the study by Huang et al., the analysis of patients with PSI classes IV/V found that patients in the highest MR-proADM quartile had significantly higher mortality at 90 days compared with patients whose MR-proADM levels were in the quartiles 1 to 3. The same did

not hold true for patients with PSI classes I to III, in which mortality was low and did not significantly change according to MR-proADM quartile. Furthermore, the addition of MR-proADM to clinical prediction rules did not significantly change the AUC for the prediction of mortality [28]. In the study with longest outcome ascertainment (18 months), the hazard of death was 1.9 higher for those with MR-proADM level between 1.22 and 1.97 nmol/l, and 3.3 higher for those with MR-proADM level > 1.97 nmol/l compared with those whose MR-proADM level was <1 nmol/l. The analysis was statistically significant and was adjusted for a number of confounders [6]. For the prediction of mortality at 180 days, Julian-Jimenez et al. reported that the AUC of MR-proADM was higher than that of clinical prediction rules [33]. In the study by Bello et al., the addition of MR-proADM to PSI led to significantly better discrimination compared with PSI alone for the prediction of 1 year mortality [4]. In a regression analysis with adjustment for CURB-65 and comorbidities, patients with increase in the MR-

**Figure 4** Forest plot of area under the receiver operating characteristic curve ratio of risk score plus midregional proadrenomedullin over risk score.





**Figure 5** Forest plot displaying meta-analysis of the odds ratio of short-term complications in patients with increased level of midregional proadrenomedullin.

proADM(log<sub>10</sub>) had a 1.9 significant increase in the hazard of 180-day mortality [7].

### Risk of bias in the included studies

The 2 items in which most studies showed a high risk of bias included “establishment of test cut-off *a priori*” and “being free of commercial funding”. Our sensitivity analysis showed the pooled results did not substantially change when the data are stratified according to these items.

### Practical application

Given the value of MR-proADM for the prediction of short-term mortality in patients with CAP, it is reasonable to expect that this test will be valuable for the guidance of hospital admission triage and discharge in these patients, and will ultimately contribute to decrease in the length of hospital stay. To test this hypothesis, Albrich et al. performed a proof-of-concept randomized intervention trial in which triage and discharge decisions for patients with lower respiratory tract infection were made by the treating physician with the help of either medical and biopsychosocial risk assessment or MR-proADM plus medical and biopsychosocial risk assessment criteria. The study

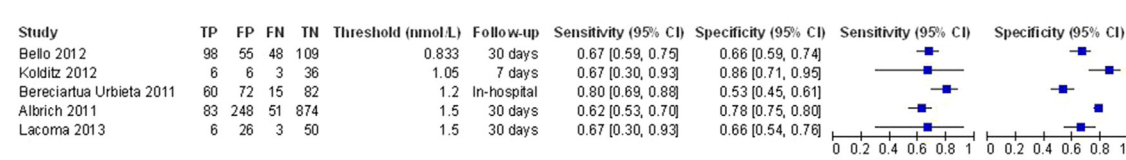
enrolled 313 patients. There was no significant difference in length of stay between the 2 groups. A limitation of this trial was that the study algorithm was overruled in 39.3% of the patients at presentation and in 34.5% during hospitalization [20].

### Limitations

Our systematic review has some limitations. Only a few studies reported on long-term term outcomes, and they described the outcomes in a heterogeneous way. In some instances of missing information, we were unable to obtain the data despite an attempt to contact the authors of the primary studies.

### Implications for future research

There is need for additional clinical trials evaluating the integration of MR-proADM- perhaps in association with other biomarkers- into clinical pathways for risk stratification of patients with CAP. A challenge is to obtain adequate adherence to a proposed clinical pathway. A way of overcoming this challenge is to carry out pilot phase studies with the goal of assessing the adherence to protocol.



**Figure 6** Forest plots displaying sensitivity and specificity of midregional proadrenomedullin for the prediction of short-term complications in patients with community-acquired pneumonia.

**Table 4** Quality items for assessment of risk of bias in the included studies.

	Christ-Crain,2006 [5]	Huang, 2009 [28]	Kruger, 2010 [7]	Guertler, 2011 [6]	Albrich, 2011 [3]	Bereciartua Urbieta, 2011 [29]	Bello, 2012 [4]	Kolditz, 2012 [30]	Suberviola, 2012 [31]	Courtais, 2013 [32]	Julian-Jimenez 2013 [33]	Lacoma, 2013 [34]
Demographic characteristic fully described	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were selection criteria clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Definition of CAP well described	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the index test obtained early in course of disease?	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the execution of the index test described in sufficient detail to permit replication of the test?	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Were withdrawals from the study explained?	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Were cut-off values established before the study was started?	No	Yes	No	Yes	No	No	No	No	No	No	No	No
Were objectives pre-specified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Mid and long —term follow up	No	Yes	Yes	Yes	No	No	Yes	No	No	No	Yes	No
Was the study free of commercial funding?	No	No	No	Yes	Yes	No	No	No	Yes	No	Yes	No

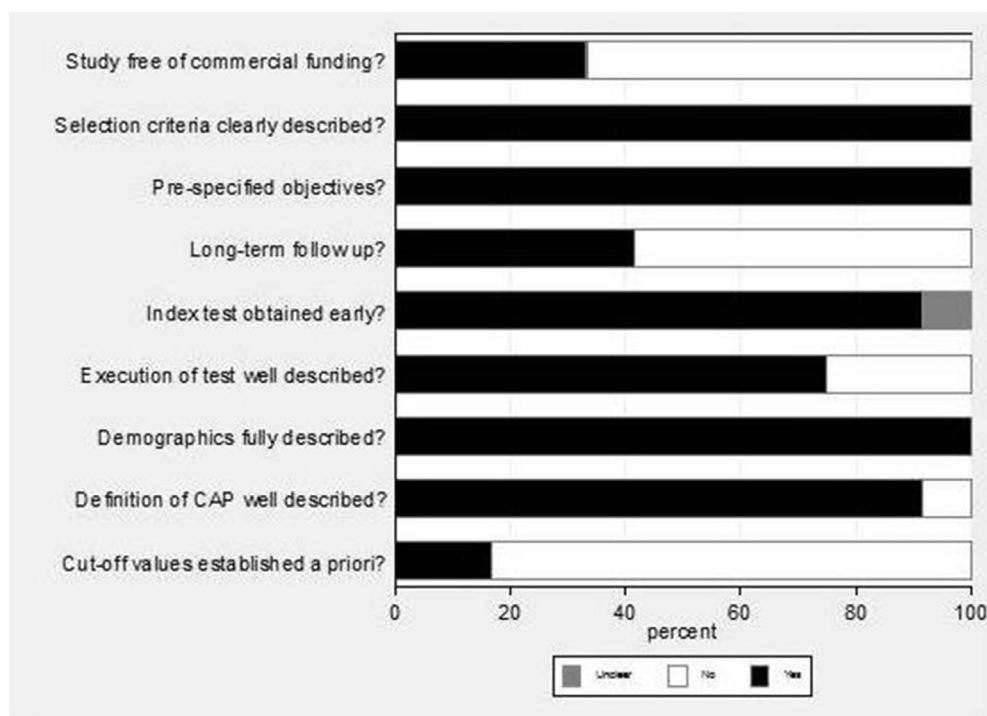


Figure 7 Risk of bias assessment of the studies included in this review.

Complex pathways with low adherence can thus be simplified before they are tested in clinical trials.

## Conclusion

Our review confirms that MR-proADM is associated with short-term mortality and complications in patients with CAP. Although the data are not nearly as robust, it also appears the MR-proADM is valuable for long-term prognosis of these patients. The combined use of MR-proADM and CURB-65/CRB-65 provides improved discriminant ability over the risk score alone. Whether the use of MR-proADM will translate into better patient outcomes is yet to be established.

## Conflict of interest

None.

## Funding

None.

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